SAM-TDR-63-38

THE ACUTE MAMMALIAN TOXICITY OF RARE EARTH NITRATES AND OXIDES

TECHNICAL DOCUMENTARY REPORT NO. 63-38

August 1963

USAF School of Aerospace Medicine
Aerospace Medical Division (AFSC)
Brooks Air Force Base, Texas

Task No. 883002

(Prepared under Contract No. AF 41(657)-1382 at the
USAF Radiation Laboratory, University of Chicago, Chicago, Illinois)

FOREWORD

This report was prepared at the USAF Radiation Laboratory, University of Chicago, Chicago, Illinois, by—

DAVID W. BRUCE
BERNARD E. HIETBRINK
KENNETH P. DuBOIS

ABSTRACT

Results of acute toxicity studies on rare earth nitrates indicate that their acute toxicity is highly dependent on the route of administration. The nitrate salts were moderately toxic when given intraperitoneally to rats and mice and only slightly toxic when administered orally to rats. With the exception of the transition elements, for which the oral LD_{50} values were greater than 5,000 mg./kg., the compounds generally exhibited an increase in toxicity with increasing atomic weight. The light lanthanons are highly toxic to rats by the intravenous route. The nitrate salts of cerium, praseodymium, neodymium, and samarium were from 7 to 11 times more toxic to females than to male rats. Erbium nitrate, a heavy lanthanon, did not show the marked sex difference in toxicity to rats. Rats were able to tolerate 1,000 mg./kg. of the rare earth oxides given orally or intraperitoneally.

This technical documentary report has been reviewed and is approved.

Robert B Payne

ROBERT B. PAYNE
Colonel, USAF, MSC
Chief, Operations Division

THE ACUTE MAMMALIAN TOXICITY OF RARE EARTH NITRATES AND OXIDES

1. INTRODUCTION

In a review of most of the available data on the acute oral, intravenous, and intraperitoneal toxicity of the rare earth compounds, Kyker and Cress (1) emphasized the need for additional experimental work on many elements of this series. Subsequent studies by Haley et al. (2) provided information on the intraperitoneal and oral toxicity of gadolinium and samarium chloride to mice and the acute intravenous toxicity of these elements to cats. A preliminary report of some of the findings described in this study has been published (3). In addition, Graca et al. (4) have reported results of intraperitoneal toxicity studies in mice and guinea pigs in which they compared the acute toxicity of the chloride salts with the citrate and ethylenediamine tetraacetic acid complexes of the stable rare earths.

The present study was undertaken to obtain additional information on the acute toxicity of rare earth nitrates and oxides to aid in the assessment of health hazards associated with the industrial and medical uses of these elements, as well as the potential hazard from the chemical toxicity of the metals as products of nuclear fission.

2. SUMMARY

Acute toxicity studies were conducted on the rare earth nitrates and oxides. The approximate LD_{50} values for the rare earth nitrates given intraperitoneally to mice ranged from 225 mg./kg. to 480 mg./kg., and for rats the values ranged from 210 mg./kg. to 335 mg./kg. Rats were able to tolerate 1,000 mg./kg. of the rare earth oxides given orally or by the intraperitoneal route. When the salts of rare earths were administered orally to rats, the LD_{50} values ranged from 2,750 mg./kg. to 4,200 mg./kg. With the exception of the transition elements for which the oral LD_{50} values were greater than 5,000 mg./kg., the compounds generally exhibited an increase in toxicity with increasing atomic weight.

Intravenous toxicity studies in rats showed that the light lanthanons are highly toxic to rats, and an appreciable sex difference in susceptibility was observed. The nitrate salts of cerium, praseodymium, neodymium, and samarium were from 7 to 11 times more toxic to females than to male rats. In contrast, erbium nitrate, a member of the heavy lanthanons, did not show the marked sex difference in toxicity to rats.

Received for publication on 7 March 1963.

3. METHODS

Animals

Adult male and female Sprague-Dawley rats (190 gm. to 250 gm.) and Carworth Farms CF_1 mice (20 gm. to 25 gm.) were used for this study. The animals were housed in air-conditioned quarters and were given water and food (Rockland Rat Diet or Rockland Mouse Pellets) ad libitum.

Rare earth compounds

The rare earth nitrates were obtained from commercial sources. The didymium nitrate, a mixture of rare earths, had the following approximate composition in terms of rare earth oxides according to the manufacturer: lanthanum 45% to 46%; neodymium 32% to 33%; praseodymium 9% to 10%; samarium 5% to 6%; gadolinium 3% to 4%; yttrium 0.4%; and other rare earths 1% to

2%. Cerium oxide (CeO_2), praseodymium oxide (Pr_6O_{11}), terbium oxide (Tb_4O_7), and other oxides with the general formula RE_2O_3 were obtained from commercial sources.

Toxicity measurements

Aqueous solutions (pH 4.0 to 5.9) of the rare earth nitrates were prepared immediately before injection. The solutions were given in single doses (a) to female mice and rats by the intraperitoneal route in volumes equivalent to 0.5% and 0.1%, respectively, of the total body weight, (b) orally by stomach tube to female rats as 50% aqueous solutions, and (c) by intravenous injection in isotonic saline via the tail vein to male and female rats in volumes equivalent to 0.1% of the total body weight. Rare earth oxides prepared as 50% suspensions by homogenization in an aqueous 0.2% solution of carboxymethylcellulose were given orally and by the intraperitoneal route to female rats as a single dose of 1,000 mg./kg. All compounds were of the highest available purity which exceeded 98% in all cases.

For the LD_{50} measurements, groups, each containing 5 or 10 animals, were given various doses of each compound and were observed for a period of 30 days. On the basis of the mortality that occurred during the 30-day observation period, the LD_{50} values with 95% confidence limits were calculated by the method of Litchfield and Wilcoxon (5).

4. RESULTS

Acute toxicity of rare earth nitrates given intraperitoneally to mice and rats

The results of toxicity tests performed by intraperitoneal administration of the rare earth nitrates to female mice are presented in table I. The LD_{50} values for the nitrate salts ranged from 225 mg./kg. for erbium nitrate to 480 mg./kg. for terbium nitrate. In terms of the metal content of the compounds these values were equivalent to 81 mg./kg. to 168 mg./kg. of the rare earth metals indicating that these metals are moderately toxic by the intraperitoneal route to female mice.

TABLE I

Acute intraperitoneal toxicity of rare earth nitrates to female mice

Nitrate compound	Number of mice	LD_{50} with 95% confidence limits	
		Compound (mg./kg.)	Metal (mg./kg.)
Didymium	35	330 (314-346)	—
Lanthanum	35	410 (353-475)	131 (113-152)
Cerium (ous)	35	470 (435-508)	151 (140-163)
Praseodymium	45	290 (259-325)	94 (84-105)
Neodymium	45	270 (221-329)	89 (73-108)
Samarium	40	315 (258-384)	106 (87-130)
Europium	30	320 (294-349)	109 (100-119)
Gadolinium	40	300 (261-345)	105 (91-120)
Terbium	45	480 (444-518)	168 (156-182)
Dysprosium	40	310 (261-369)	110 (93-131)
Holmium	45	320 (302-339)	115 (108-122)
Erbium	55	225 (194-261)	81 (70-95)
Thulium	45	255 (226-288)	93 (82-105)
Ytterbium	45	250 (185-338)	93 (68-125)
Lutetium	30	290 (259-325)	108 (97-121)

Most of the mice that were acutely poisoned became depressed within an hour after injection. The animals that remained in a depressed state for a period of 8 hours usually died within the first 24 hours. With the exception of lutetium, the time-mortality pattern was the same for all rare earth compounds with 79% of the deaths occurring during the first 4 days and 94% of the mortality occurring within the first 8 days after injection. Lutetium caused significant mortality (26%) between the

TABLE II

Acute intraperitoneal toxicity of rare earth nitrates to female rats

Nitrate compound	Number of rats	LD_{50} with 95% confidence limits	
		Compound (mg./kg.)	Metal (mg./kg.)
Didymium	30	270 (241-302)	—
Cerium (ous)	30	290 (238-354)	93 (77-114)
Praseodymium	30	245 (209-287)	79 (68-93)
Neodymium	30	270 (231-316)	89 (76-104)
Samarium	30	285 (254-319)	96 (86-108)
Europium	30	210 (172-256)	72 (59-87)
Gadolinium	40	230 (204-260)	80 (71-91)
Terbium	30	260 (232-291)	91 (81-102)
Dysprosium	30	295 (236-369)	105 (84-131)
Holmium	30	270 (237-308)	97 (85-111)
Erbium	35	230 (195-271)	83 (71-98)
Thulium	25	285 (252-322)	104 (92-117)
Ytterbium	30	255 (220-296)	94 (81-110)
Lutetium	30	335 (294-382)	125 (110-142)

eighth and thirtieth day after intraperitoneal administration. Most of the animals that survived the 30-day observation period after treatment with the various rare earths appeared normal on gross examination; however, postmortem examination of randomly selected animals showed generalized peritonitis with adhesions and accumulation of some ascitic fluid.

Table II summarizes the acute intraperitoneal toxicity of rare earth nitrates to female rats. The LD_{50} values ranged from 210 mg./kg. to 335 mg./kg. for the various compounds. In terms of the metal content of the compounds the LD_{50} values ranged from 72 mg./kg. for europium to 125 mg./kg. for lutetium. Thus, the LD_{50} values were in the same range as those for mice. Preliminary experiments indicated no sex difference in the susceptibility of rats to these metals given intraperitoneally.

Although no definite time-mortality pattern was observed, very few of the rats that received lethal doses died during the first 8 days. Most mortalities occurred during the period from 10 to 25 days after injection. Almost all the animals that died during this period had grossly distended abdomens, and edema of the limbs was observed in many of the animals that received the higher doses. Gross pathologic examination of the animals revealed an inflammatory condition in the peritoneal cavity with massive adhesions and accumulation of hemorrhagic ascitic fluid. These observations agree with the more detailed pathologic findings of Steffee (6) with the rare earth chlorides.

In an attempt to determine whether the toxicity of the nitrate ion contributes to the toxicity of the nitrate salts of rare earths, a dose of 1.67 mM./kg. of sodium nitrate adjusted to pH 5 was given to a group of 10 female rats. This dose is equivalent to the amount of nitrate in lutetium nitrate which was the least toxic of the compounds included in this study to rats. No mortality or gross pathologic changes were observed in any of the animals during the 30-day observation period.

Acute oral toxicity of rare earth nitrates to female rats

The acute oral toxicity of rare earth nitrates to female rats is shown in table III. The LD_{50} values ranged from 2,750 mg./kg. for neodymium nitrate to 4,200 mg./kg. for cerium nitrate. These values for the salts are equivalent to 905 mg./kg. to 1,355 mg./kg., respectively, for the metals, thus indicating that these elements have low acute toxicity by the oral route. The transition elements or

TABLE III

Acute oral toxicity of rare earth nitrates to female rats

Nitrate compound	Number of rats	LD_{50} with 95% confidence limits	
		Compound (mg./kg.)	Metal (mg./kg.)
Didymium	30	4100 (3628-4633)	—
Cerium (ous)	30	4200 (3684-4788)	1355 (1189-1545)
Praseodymium	35	3500 (3017-4060)	1134 (977-1315)
Neodymium	30	2750 (1896-3988)	905 (624-1312)
Samarium	30	2900 (2660-3161)	981 (890-1069)
Europium	20	> 5000	> 1704
Gadolium	20	> 5000	> 1743
Terbium	35	> 5000	> 1753
Dysprosium	25	3100 (2870-3348)	1103 (1027-1192)
Holmium	25	3000 (2804-3210)	1078 (1007-1153)
Ytterbium	35	3100 (2924-3286)	1148 (1083-1217)

terbium group, so-called because of their difference in solubility as the double alkali sulfates, were found to have LD_{50} values greater than 5,000 mg./kg. by the oral route. In tracer studies with rats, Durbin et al. (7) found that the transition elements and lanthanum were absorbed at a slower rate from the site of intramuscular injection than the other rare earth elements which they studied. In the present study, the lighter elements (cerium through samarium) tend to show an increase in toxicity with increasing atomic weight. Cochran et al. (8) obtained an LD_{50} of 4,500 mg./kg. for lanthanum nitrate given orally to rats. In the present study, it was found that the oral LD_{50} of didymium nitrate, which is composed principally of lanthanum nitrate and neodymium nitrate, was 4,100 mg./kg., which is between the LD_{50} values obtained for the nitrates of lanthanum and neodymium. The heavy lanthanons (dysprosium, holmium, and ytterbium) appear to be of the same relative toxicity, according to the data in table III.

Within 1 to 2 hours after oral administration of the rare earth nitrates most of the rats were depressed, and animals that received lethal doses showed little activity during the survival period. The animals were observed for 30 days, although no deaths occurred later than 4 days after administration of the nitrate salts by the oral route. Throughout the observation period no gross pathologic changes were noted.

Acute intravenous toxicity of rare earth nitrates to rats

The results of studies of acute intravenous toxicity on the nitrate salts of rare earth metals are presented in table IV. These data show that there is a definite sex difference in the susceptibility of rats to the light lanthanons by this route of administration. Thus, females were approximately 11 times more susceptible than males to cerium nitrate, 10 times more susceptible to praseodymium nitrate and neodymium nitrate, and 7 times more susceptible to samarium nitrate. In contrast, a much smaller sex difference in susceptibility was noted with erbium nitrate, a member of the heavy lanthanons, as evidenced by LD_{50} values of 36 mg./kg. and 52 mg./kg. for females and males, respectively.

Some preliminary experiments were conducted on the intravenous toxicity of europium, gadolinium, terbium, dysprosium, holmium, and ytterbium nitrates to female rats. The data suggested that the LD_{50} values for these compounds expressed in terms of the metal content would lie in the range of 20 to 40 mg./kg. Deaths occurred within 5 days after injection of the light lanthanons and the highest mortality was noted 48 to 84 hours after injection. Europium and dysprosium appeared to be the most toxic by this route. For the other members of the series, mortality occurred throughout the 30-day observation period.

TABLE IV

Acute intravenous toxicity of rare earth nitrates to adult rats

Nitrate compound	Sex	Number of rats	LD_{50} with 95% confidence limits	
			Compound (mg./kg.)	Metal (mg./kg.)
Cerium (ous)	F	20	4.3 (3.4-5.6)	1.4 (1.1-1.8)
	M	35	49.6 (32.8-74.4)	16.0 (10.6-24.0)
Praseodymium	F	25	7.4 (5.1-10.8)	2.4 (1.7-3.5)
	M	25	77.2 (49.7-119.8)	25.0 (16.1-38.8)
Neodymium	F	40	6.4 (5.5-7.3)	2.1 (1.8-2.4)
	M	25	66.8 (53.5-83.6)	22.0 (17.6-27.5)
Samarium	F	30	8.9 (6.8-11.8)	3.0 (2.3-4.0)
	M	20	59.1 (40.5-86.3)	20.0 (13.7-29.2)
Erbium	F	25	35.8 (27.8-49.9)	13.0 (9.9-18.1)
	M	25	52.4 (37.0-74.5)	19.0 (13.4-27.0)

Acute oral and intraperitoneal toxicity of rare earth oxides

Female rats were given 1,000 mg./kg. of the oxides of all of the metals listed in table II except didymium by the intraperitoneal and oral routes, and the animals were observed for 30 days. Except for an occasional death, the animals were able to tolerate 1,000 mg./kg. of the rare earth oxides, and the LD_{50} values for the oxides are, therefore, in excess of this dosage level for all of the compounds that were tested.

5. DISCUSSION

The present investigation was undertaken to expand the available information on the acute toxicity of the rare earth metals. The results of this study have indicated that the acute toxicity of rare earth nitrates is highly dependent on the route of administration. Thus, the rare earth nitrates exhibit moderate toxicity by the intraperitoneal route to mice and rats. When they were given by the oral route, however, the toxicity was much lower. Poor absorption from the gastrointestinal tract (9) and peritoneal cavity is undoubtedly a major factor in limiting the toxicity by these routes, because those compounds that were given by the intravenous route exhibited high toxicity. If the LD_{50} values can be used as an index of absorption, they suggest, except in the case of the transition elements, that the amount absorbed is related to the relative basicity of the compounds (10).

Comparison of the acute toxicity of the rare earth nitrates given intraperitoneally to

rats and mice indicated that rats are somewhat more susceptible to most of the compounds than mice. Most of the deaths among mice occurred during the first 4 days after injection, whereas the deaths in rats were more delayed.

When the nitrate salts of the light lanthanons (cerium, praseodymium, neodymium, and samarium) were given intravenously, female rats were 7 to 11 times more susceptible than males. The possibility of a sex difference in susceptibility was suggested by the studies of Snyder et al. (11, 12) who found that a 3.5 mg./kg. dose of cerium chloride produced a two-fold increase in the liver lipids in female and castrated male rats but no significant change in the liver lipid content in normal males. This elevation in the liver lipids was also found in female rats that received the other light lanthanons, but not in females given a similar dose of the heavy lanthanons.

Our studies and those of Kyker and Cress (1) suggest that the intravenous toxicity of the ionic compounds of the rare earths decreases with increasing atomic weight. Aeberhardt et al. (13) found a difference in the initial distribution during studies on the metabolism of intravenously administered ionic and colloidal cerium 144 in rats. The ionic cerium (pH 4) was fixed by the hepatocytes and excreted by way of the bile without reabsorption, while the colloidal compound (pH 10) was first fixed by the reticuloendothelial system and then transferred to the bone tissue and the hepatocytes. These studies with cerium 144 indicated that the ionic cerium is bound, possibly to plasma proteins, while the colloidal form is not bound. Since the solubility of a given concentration of the trivalent lanthanons would tend to decrease in the order of increasing atomic weight, the tendency of these compounds to precipitate when injected intravenously as aqueous solutions would also increase. If this is the case, it may account, at least in part, for the difference in distribution and toxicity of the light and heavy lanthanons.

REFERENCES

1. Kyker, G. C., and E. A. Cress. Acute toxicity of yttrium, lanthanum, and other rare earths. A.M.A. Arch. Industr. Health 16:475-479 (1957).
2. Haley, T. J., K. Raymond, N. Komesu, and H. C. Upham. Toxicological and pharmacological effects of gadolinium and samarium chlorides. Brit. J. Pharmacol. 17:526-532 (1961).
3. Hietbrink, B. E., D. W. Bruce, and K. P. DuBois. The acute oral and intraperitoneal toxicity of rare earth compounds. Fed. Proc. 20:435 (1961).
4. Graca, J. G., F. C. Davidson, and J. B. Feavel. Comparative toxicity of stable rare earth compounds. II. Effect of citrate and edetate complexing on acute toxicity in mice and guinea pigs. Arch. Environ. Health 5:437-444 (1962).
5. Litchfield, J. T., Jr., and F. Wilcoxon. A simplified method of evaluating dose-effect experiments. J. Pharmacol. Exp. Ther. 96:99-113 (1949).
6. Steffee, C. H. Histopathologic effects of rare earths administered intraperitoneally to rats. A.M.A. Arch. Industr. Health 20:414-419 (1959).
7. Durbin, P. W., M. H. Williams, M. Gee, R. H. Newman, and J. G. Hamilton. Metabolism of the lanthanons in the rat. Proc. Soc. Exp. Biol. Med. 91:78-85 (1956).
8. Cochran, K. W., J. Doull, M. Mazur, and K. P. DuBois. Acute toxicity of zirconium, columbium, strontium, lanthanum, cesium, tantalum and yttrium. Arch. Industr. Hyg. and Occupational Med. 1:637-650 (1950).
9. Hamilton, J. G. The metabolism of the radioactive elements created by nuclear fission. New Eng. J. Med. 240:863-870 (1949).
10. Kremers, H. E. Hydrolytic reactions of the rare earths. U. S. Atom. Energy Comm. ORINS-12, 12-23 (1956).
11. Snyder, F., E. A. Cress, and G. C. Kyker. Liver lipid response to intravenous rare earths in rats. J. Lipid Res. 1:125-131 (1959).
12. Snyder, F., E. A. Cress, and G. C. Kyker. Rare-earth fatty liver. Nature 185:480-481 (1960).
13. Aeberhardt, A., P. Nizza, J. Remy, and Y. Boilleau. Etude comparee du métabolisme du cérium 144 en fonction de son état physico-chimique chez le rat. Int. J. Radiat. Biol. 5:217-246 (1962).

USAF School of Aerospace Medicine, Brooks AF Base, Tex.

SAM-TDR-63-38. THE ACUTE MAMMALIAN TOXICITY OF RARE EARTH NITRATES AND OXIDES. Aug. 63, 6 pp. incl. tables, 13 refs.

Unclassified Report

Results of acute toxicity studies on rare earth nitrates indicate that their acute toxicity is highly dependent on the route of administration. The nitrate salts were moderately toxic when given intraperitoneally to rats and mice and only slightly toxic when administered orally to rats. With the exception of the transition elements, for which the oral

1. Toxicity
2. Pharmacology
3. Chemistry

I. Task 583002
II. Contract No. AF 41(609)-1693
III. U. of Chicago, Chicago, Ill.
IV. D. W. Bruce, B. E. Hietbrink, K. P. DuBois
V. In ASTIA collection

USAF School of Aerospace Medicine, Brooks AF Base, Tex.

SAM-TDR-63-38. THE ACUTE MAMMALIAN TOXICITY OF RARE EARTH NITRATES AND OXIDES. Aug. 63, 6 pp. incl. tables, 13 refs.

Unclassified Report

Results of acute toxicity studies on rare earth nitrates indicate that their acute toxicity is highly dependent on the route of administration. The nitrate salts were moderately toxic when given intraperitoneally to rats and mice and only slightly toxic when administered orally to rats. With the exception of the transition elements, for which the oral

1. Toxicity
2. Pharmacology
3. Chemistry

I. Task 583002
II. Contract No. AF 41(609)-1693
III. U. of Chicago, Chicago, Ill.
IV. D. W. Bruce, B. E. Hietbrink, K. P. DuBois
V. In ASTIA collection

USAF School of Aerospace Medicine, Brooks AF Base, Tex.

SAM-TDR-63-38. THE ACUTE MAMMALIAN TOXICITY OF RARE EARTH NITRATES AND OXIDES. Aug. 63, 6 pp. incl. tables, 13 refs.

Unclassified Report

Results of acute toxicity studies on rare earth nitrates indicate that their acute toxicity is highly dependent on the route of administration. The nitrate salts were moderately toxic when given intraperitoneally to rats and mice and only slightly toxic when administered orally to rats. With the exception of the transition elements, for which the oral

1. Toxicity
2. Pharmacology
3. Chemistry

I. Task 583002
II. Contract No. AF 41(609)-1693
III. U. of Chicago, Chicago, Ill.
IV. D. W. Bruce, B. E. Hietbrink, K. P. DuBois
V. In ASTIA collection

USAF School of Aerospace Medicine, Brooks AF Base, Tex.

SAM-TDR-63-38. THE ACUTE MAMMALIAN TOXICITY OF RARE EARTH NITRATES AND OXIDES. Aug. 63, 6 pp. incl. tables, 13 refs.

Unclassified Report

Results of acute toxicity studies on rare earth nitrates indicate that their acute toxicity is highly dependent on the route of administration. The nitrate salts were moderately toxic when given intraperitoneally to rats and mice and only slightly toxic when administered orally to rats. With the exception of the transition elements, for which the oral

1. Toxicity
2. Pharmacology
3. Chemistry

I. Task 583002
II. Contract No. AF 41(609)-1693
III. U. of Chicago, Chicago, Ill.
IV. D. W. Bruce, B. E. Hietbrink, K. P. DuBois
V. In ASTIA collection

LD_{50} values were greater than 5,000 mg./kg., the compounds generally exhibited an increase in toxicity with increasing atomic weight. The light lanthanons are highly toxic to rats by the intravenous route. The nitrate salts of cerium, praseodymium, neodymium, and samarium were from 7 to 11 times more toxic to females than to male rats. Erbium nitrate, a heavy lanthanon, did not show the marked sex difference in toxicity to rats. Rats were able to tolerate 1,000 mg./kg. of the rare earth oxides given orally or intraperitoneally.

LD_{50} values were greater than 5,000 mg./kg., the compounds generally exhibited an increase in toxicity with increasing atomic weight. The light lanthanons are highly toxic to rats by the intravenous route. The nitrate salts of cerium, praseodymium, neodymium, and samarium were from 7 to 11 times more toxic to females than to male rats. Erbium nitrate, a heavy lanthanon, did not show the marked sex difference in toxicity to rats. Rats were able to tolerate 1,000 mg./kg. of the rare earth oxides given orally or intraperitoneally.

LD_{50} values were greater than 5,000 mg./kg., the compounds generally exhibited an increase in toxicity with increasing atomic weight. The light lanthanons are highly toxic to rats by the intravenous route. The nitrate salts of cerium, praseodymium, neodymium, and samarium were from 7 to 11 times more toxic to females than to male rats. Erbium nitrate, a heavy lanthanon, did not show the marked sex difference in toxicity to rats. Rats were able to tolerate 1,000 mg./kg. of the rare earth oxides given orally or intraperitoneally.

LD_{50} values were greater than 5,000 mg./kg., the compounds generally exhibited an increase in toxicity with increasing atomic weight. The light lanthanons are highly toxic to rats by the intravenous route. The nitrate salts of cerium, praseodymium, neodymium, and samarium were from 7 to 11 times more toxic to females than to male rats. Erbium nitrate, a heavy lanthanon, did not show the marked sex difference in toxicity to rats. Rats were able to tolerate 1,000 mg./kg. of the rare earth oxides given orally or intraperitoneally.